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Treatment of Diabetic Patients

Observations on the Use of Carbutamide and Tolbutamide

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• **Of a group of 32 patients with diabetes, 26 had a favorable modification of the disease in response to administration of butyl-sulfonylurea. All but one of the patients who had good response were past the age of 38. All diabetic patients included in this group were those with little or no tendency to ketosis after cessation of insulin administration. No toxic manifestations were noted except for a slight decrease in leukocytes in one case.**

RECENT REPORTS have indicated that certain butyl sulfonylurea compounds, specifically carbutamide (BZ-55) and tolbutamide (Orinase®), differing chemically from each other only in the substitution of a methyl group on the benzene ring in the latter compound as compared to an amino group in the former, produce favorable modification in the diabetic state in a high percentage of middleaged patients with diabetes.[1-11] The present report represents observations in 32 such patients who have been observed in the outpatient department of the Highland Alameda County Hospital.

Many of these patients were in the "noncooperative" category; that is, they did not adhere to any dietary program. All of them had significant hyperglycemia. Many were receiving appreciable amounts of insulin.

Prior to administration of sulfonamide, insulin was discontinued gradually or abruptly. Ketonuria developed with discontinuance of insulin in only one of the patients studied. In the majority, hyperglycemia varied in surprisingly slight degree from that noted during the period of insulin administration.

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After a period of two weeks or less following discontinuance of insulin, sulfonamide administration was begun in a dosage ranging from 0.5 to 4.0 gm. daily. Subsequent dosage was increased or decreased as indicated by the blood sugar response. The usual maintenance dose was 1 gm. daily.

In addition to measurement of sugar in the blood and in the urine, the patients were also studied with regard to 24-hour iodine^{131} uptake, and leukocyte and differential blood counts.

The results of the study (extending over the period March to July, 1956) are shown in Table 1 and Chart 1. Of this group of 32 patients, 26 or 81 per cent showed a significant response to sulfonamide therapy. Of the 26, 13 showed significant, but slight, response—*i.e.*, a drop in the fasting blood sugar of less than 50 mg. per 100 cc.; nine manifested a moderate response, with a decrease in fast-

TABLE 1.—*Clinical and Laboratory Data in 32 Diabetic Patients Receiving Carbutamide or Tolbutamide*

Patient: Age, Race, Sex	Years Diabetic	Severity	Stability	Obesity	Previous Dose Insulin (units)	Blood Sugars (Fasting) on Insulin (Milligrams per 100 cc.)	Blood Sugars (Fasting) Without Insulin (Milligrams per 100 cc.)	Sulfonamide Therapy: Blood Sugar (Fasting)	Initial Dose (gm.)	Maintenance Dose (gm.)	Blood Sulfa (Mg. per 100 cc.)	Duration of Therapy (Weeks)	Toxicity	Associated Diseases and Other Medications
69 WF	16	Mild	+	Mild	30 NPH	100 to 200	157 to 218	86 to 96	1.0	.5	....	3	....	Arteriosclerosis obliterans, on thyroid, 100 mg. daily
72 WF	2	Mild	+	....	....	....	175	80 to 100	.5	.5	7 to 13	11	....	Hypertensive heart disease, on Rauwolfia
56 NM	8	Mild	±	Mild	20 NPH	200 to 350	150 to 250	150 to 350	2.0	3.0	7 to 15	11	....	
72 WF	16	Mild	+	....	15 PZI	140 to 220	150 to 240	105 to 130	.5	1.0	11 to 13	9	....	
49 WF	7	Mild	+	Mild	20 NPH	90 to 210	170 to 220	120 to 150	1.0	1.0	7 to 9	9	....	Recent partial loss of vision, prior to therapy
71 WF	8	Mild	+	....	30 NPH	120 to 270	170	80 to 125	2.0	.5	4 to 12	14	....	Arteriosclerotic heart disease; carcinoma of cervix
54 WM	1/3	Mild	+	....	20 NPH	130 to 200	110 to 200	95 to 120	1.0	1.0	4 to 7	10	....	Cirrhosis
38 NF	¼	Mild	+	Marked		....	140 to 235	80 to 95	2.0	1.0	6 to 10	14	granulopenia	Late latent syphilis
53 NF	8	Mild	+	Moderate	40 PZI	145 to 350	175 to 375	90 to 170	2.0	1.0	5 to 14	16	....	
63 WF	11	Mild	+	....	15 PZI	100 to 170	105 to 165	75 to 90	1.0	.5	6 to 12	16	....	Cerebrovascular disease
55 WF	4	Mild	+	....	20 NPH*	125	250 to 300	100 to 135	2.0	.5	8 to 13	12	....	Pyelonephritis, 1952; albuminuria, now present
77 WM	7	Moderate	+	Mild	40 NPH	160 to 210	160 to 260	95 to 165	1.0	1.0	7 to 12	18	....	Enlarged liver; alcoholic history
56 WF	7	Moderate to Severe	—	Mild	40 NPH	290 to 440	300 to 325	190 to 225	4.0	1.0	6 to 16	1½	....	Arteriosclerotic heart disease, old infarct.; chronic cholecystitis; cont. glycosuria + ketonuria on carbutamide therapy
48 NF	½	Moderate	+	Mild	10 NPH	150 to 300	150 to 225	85 to 130	1.5	.5	5 to 11	16	....	
51 NF	7	Mild	+	Moderate	15 NPH	140 to 200	....	70 to 90	2.0	.5	8 to 13	21	....	Arrested pulmonary tuberculosis; no treatment since January, 1956
46 NF	½	Mild	+	....	....	....	115 to 160	70 to 95	2.0	.5	2 to 12 (4 to 6)	7	....	
55 WF	3	Mild	+	Mild	....	....	220 to 240	80 to 100	1.5	.5	6 to 12	16	....	

*1952 only.

TABLE 1 (Continued)

Patient: Age, Race, Sex	Years Diabetic	Severity	Stability	Obesity	Previous Dose Insulin (units)	Blood Sugars (Fasting) on Insulin (Milligrams per 100 cc.)	Blood Sugars (Fasting) Without Insulin (Milligrams per 100 cc.)	Sulfonamide Therapy: Blood Sugar (Fasting)	Initial Dose (gm.)	Maintenance Dose (gm.)	Blood Sulfa (Mg. per 100 cc.)	Duration of Therapy (Weeks)	Toxicity	Associated Diseases and Other Medications
68WF	13	Mild	+	Moderate	30 NPH	155 to 180	180	190 to 225	1.0	1.0	....	4	....	
62WF	13	Mild	+	Moderate	10 NPH	180 to 220	....	85 to 110	1.5	.5	7 to 13	16	....	General arteriosclerosis; old cerebrovascular accident
54 WF	16	Mild	+	Moderate	30 NPH	190 to 390	120 to 190	100 to 110	.5	.5	4 to 7	9	....	Cirrhosis; peripheral neuritis
65 WF	19	Mild	+	Marked	10 NPH	180 to 240	180 to 205	75 to 105	2.0	.5	5 to 13	13	....	Arteriosclerotic heart disease
55 NF	9	Moderate	±	Mild	30 Req. 30 NPH	230 to 325	160 to 260	115 to 175	2.0	.5	6 to 12	16	....	Arteriosclerotic heart disease; cerebral arteriosclerosis; pyelonephritis; cholelithiasis
19 WF	½	Moderate	±	Moderate	20 NPH	250 to 325	160 to 350	140 to 175	2.0	1.0	11 to 17	16	....	
57 NF	7	Mild	+	Mild	15 NPH	160 to 220	120 to 160	74	.5	.5	9	3	....	Hypertensive arteriosclerotic heart disease; arteriosclerosis obliterans of legs; late latent syphilis
68 WM	6	Mild	+	....	10 NPH	125 to 170	121	85 to 170	1.0	1.0	9	3	....	Hypertensive heart disease, old infarct.; arteriosclerosis obliterans both legs
48 NF	3	Mild	+	Marked	15 NPH	180 to 320	110 to 250	110 to 190	3.0	1.0	8 to 15	13	....	
60 NF	5	Mild	+	Marked	....	....	200 to 250	115 to 125	1.0	1.0	11	4	....	
41 NF	....	Moderate	±	Moderate	....	....	440	100 to 125	1.0	.5	....	8	....	Tolbutamide
73 WM	3	Moderate	+	....	50 NPH	120 to 170	145 to 180	105 to 135	1.0	1.0	....	4	....	Deafness; early cerebral arteriosclerosis; tolbutamide
64 WF	7	Moderate	+	Mild	40 NPH	255 to 325	315	245 to 340	2.0	3.0	....	4	....	Cataracts removed 1 year ago; tolbutamide
54 WF	13	Moderate	±	....	40 NPH	200 to 300	230 to 305	125 to 262	1.5	1.0	....	11	....	Arteriosclerotic heart disease with congestive failure; cerebrovascular arteriosclerosis; tolbutamide
68 WM	10	Moderate	±	Mild	20 NPH	170 to 205	170	115 to 130	3.0	1.0	....	5	....	Hypertensive arteriosclerotic heart disease with congestive failure; tolbutamide

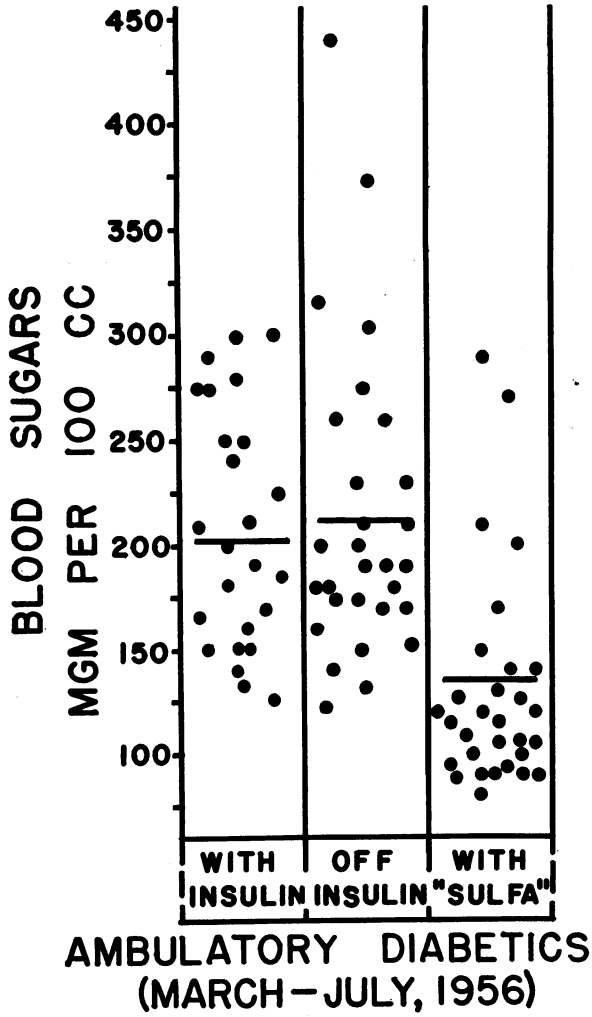

Chart 1

ing blood sugar of from 50 to 100 mg. per 100 cc.; and four had a decrease in fasting blood sugar of more than 100 mg. per 100 cc.

There appeared to be no direct correlation between presence or absence of obesity and degree of response. All the responsive patients, with the exception of a 19-year-old obese girl (with diabetes of recent origin) were over the age of 38, the eldest being 77. Only four of the six male diabetic patients had a significant response. No obvious correlation existed between the duration of the diabetes or the amount or duration of insulin treatment.

The effective blood levels of sulfonamide ranged from 4 to 14 mg. per 100 cc.

Significant decrease in iodine^{131} uptake has not been observed in patients in this group, thus far. Inhibition of iodine uptake, however, has been observed under other circumstances.[5] Some apparent decrease in leukocytes was noted in one patient after six weeks of medication with carbutamide. No subjective toxicity appeared. The patient had had moderate leukopenia before sulfonamide therapy was instituted.

Several patients appeared to have increased well being, diminished hunger, and, in some instances, weight loss, while not taking insulin and/or on sulfonamide. This statement must be interpreted cautiously, inasmuch as these patients were receiving a large amount of medical attention, which may have had some psychotherapeutic value.

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